"Drug Metabolizing Enzymes and Pharmacogenomic Testing"
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CYP2C19

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CYP2C19

- Background
- *In vitro/ in vivo* correlations
- *In vivo* genotype/ phenotype correlations
- Which alleles to measure
- Bridging between different ethnic groups
- Clinical relevance
- Conclusion

Background

- Stereoselective metabolism of the anticonvulsant mephenytoin
- Sedated volunteer, nonstereoselective metabolism
- A new drug hydroxylation polymorphism [Kupfer & Preisig –84]
- S-mephenytoin hydroxylase, functionally altered in PM [Meier & Meyer –87]
- CYP2C19 [Wrighton -93 & Goldstein –94]
- Caucasian (~3%), Asian/Oriental (~15%), African/Black (~3%), Cuna Indians in Peru (0%), Vanuatuans in the Pacific (~70%)

Background

- Autosomal recessive trait - single base pair mutation
- wt/wt, wt/m1, wt/m2, (wt/m3?), m1/m1, m1/m2 [1998]
- CYP2C19*1 (wt) – CYP2C19*15 (m14) [2002]
- EM = wt/wt + wt/m; PM = m/m
- Asian/Orientals 2x more EM wt/m than Caucasians or African/Blacks
- Ultra-rapid metabolizers, non-responders!?

Background

CYP2C19 substrates

S-mephenytoin, amitriptyline, antipyrine, carisoprodol, chlorproguanil, citalopram, clomipramine, cycloguanil, cyclophosphamide,desogestrel, diazepam, desmethyl-diazepam, flunitrazepam, fluoxetine, hexobarbital, ifosfamide, imipramine, lansoprazole, methylphenytoin, mephobarbital, moclobemid, nelfinavir, nirvanol, nortriptyline, omeprazole, omeprazole sulphone, pantoprazole, phenobarbital, phenytoin, progesterone, proguanil, propranolol, rabeprazole, seratrodast, sertraline, testosterone, thioridazine, tolbutamide, trimipramine, valproic acid, venlafaxine, R-warfarin

In vitro/ in vivo correlations

<u>Bacterial expression system (Vector pCW Ori+)</u>

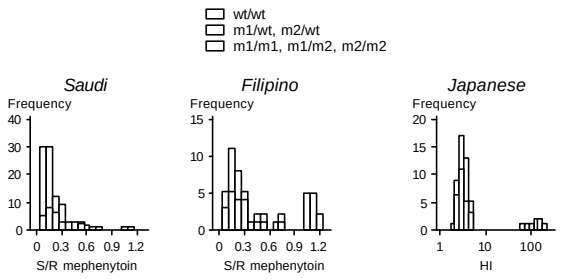
- CO binding spectra; 2C19*5A < 2C19*1A
- Western blot; 2C19*5A < 2C19*1A (40% less)
- S-MPH act. in rec. CYPs; 2C19*5A < 2C19*1A (38 vs 0.14)

Ibeanu et al 1998a

In vivo genotype/ phenotype correlations

- Mephenytoin
- Proguanil
- PPIs, e.g. omeprazole, lansoprazole, R-omeprazole

Mephenytoin



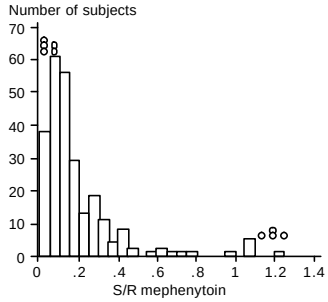
Goldstein et al 1997

Proguanil

	CYP2C19 Genotype				
	*1/*1	*1/*2	*2/*2	*2/*3	
n	4	10	4	1	
% CG	8.16	4.46	1.14	1.14	<0.05
	(6.19-10.66)	(2.35-8.13)	(0.5-1.88)		
MR	1.80	3.59	12.62	13.52	<0.05
	(1.11-3.00)	(1.46-6.04)	(7.89-41.02)		
§ Mann Whitney U test		*1/*1 vs *1/*2,	*1/*1 vs *2/*2,	*1/*2 vs *2/*2	

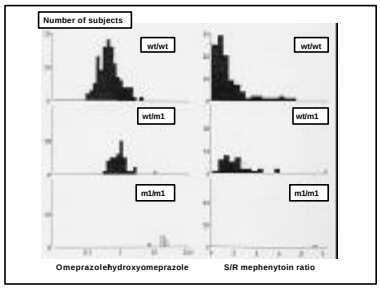
Gross et al 1997

Omeprazole



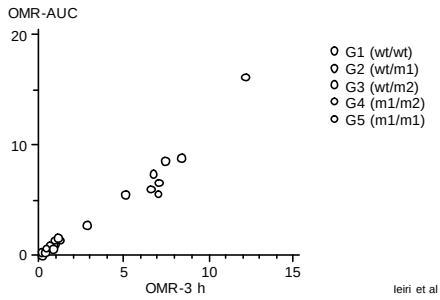
Andersson et al 1990

Omeprazole



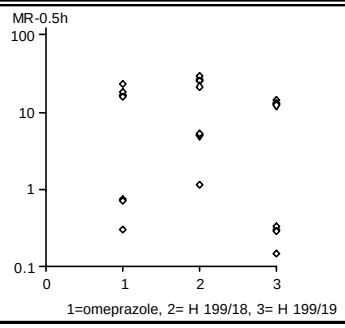
Chang et al 1995

Omeprazole

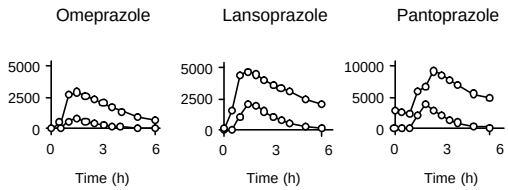


leiri et al 1996

Omeprazole-enantiomer

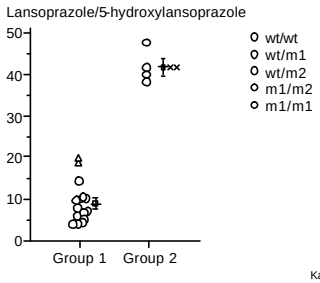


Omeprazole, Lansoprazole and Pantoprazole



Andersson et al 1998

Lansoprazole



Katsuki et al 1997

Which alleles to measure?

Allele	Enzyme activity	Caucasian PM alleles; %	Oriental PM alleles; %	African/ Black PM alleles; %
*1 (A, B, C)	Yes	-	-	-
*2 + *3	No	86.5 + 1.5 [84% of PM]	>99 (75 + 25)	~90
*4	No	3 [86% of PM]	x	x
*5	No	1 [89% of PM]	0.25	x
*6	No	~1 [92% of PM]		
*7	No	~1		
*8	~No	x		
*9 &*10	?			x
*11	?	x		
*12-*15	?			x

Blaisdell et al 2002…

Which alleles to measure?

- If including *2 &*3 ~84% of Caucasian PMs and ~99% of Oriental PMs identified
- If adding also *4, *5, and *6, ~92% of Caucasian PMs identified
- Cost benefit?

Bridging between different ethnic groups

- For drugs mainly metabolized by the well characterized CYP2C19, bridging between different ethnic groups would be appropriate and studies using just small numbers of volunteers would suffice.
- All drugs so far identified as CYP2C19 substrates are metabolized poorly in PMs, irrespective of defect alleles or ethnic origin (CYP2C9).
- The only factor that seems to determine the difference in exposure between EMs and PMs for CYP2C19 substrates is the proportion metabolized by CYP2C19
- PMs = only individuals with 2 null alleles

Clinical relevance

Treatment with CYP2C19 substrates (safety vs efficacy)

- Antidepressants (TCAs, SSRIs)
- Anticonvulsants, hypnosedatives (barbiturates, phenytoin, diazepam)
- Miscellaneous (warfarin, proguanil)
- PPIs (omeprazole, lansoprazole)

CYP2C19 associated diseases (inherited/ drug induced)

- *Bladder & lung cancer, scleroderma, Parkinson's disease, leukaemia, severe psoriasis, chronic liver disease, prostate cancer* [no clear evidence]

Clinical relevance

TCAs

- Amitriptyline, clomipramine, imipramine, trimipramine, consistently higher plasma levels in CYP2C19 PMs than in EMs
- Direct correlation between metabolizer status and adverse effect frequency has not been demonstrated, but risk if also CYP2D6 PM

SSRIs

- Sertraline, fluoxetine, and citalopram, lower (30-55%) CL in CYP2C19 PMs than in EMs [Wang et al 2001, Liu et al 2001, Sindrup et al 1993]
- Higher frequency of adverse effects have been reported in CYP2C19 PMs [Wang et al 2001]

Clinical relevance

Barbiturates

- Hexobarbital (higher plasma levels and more pronounced sedation in PMs), mephobarbital (adverse effects seemed more frequent in Japanese than in Caucasians), phenobabital (mephobarbital metabolite; not consistently slower metabolism in PMs)

Knodell et al 1988; Nakamura et al 1985; Daniel et al 1996; Desta et al 2002

Clinical relevance

Phenytoin

- Mainly a CYP2C9 substrate, but partly metabolized by CYP2C19 (*R*-4HPPH formation). Inconsistent results on gene dose effect on the total metabolism, but a study in 134 Japanese patients suggests so [pl. conc. 19, 23, 29; Mamiya et al 1998]
- However, can change from 1st order to 0 order elimination, and CYP2C9 PMs may potentially be at risk for high phenytoin exposure if also CYP2C19 PMs or inhibited via CYP2C19

Warfarin

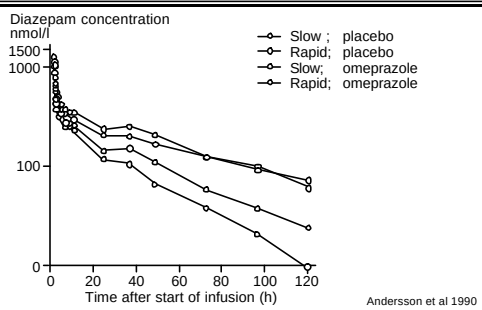
- Mainly a CYP2C9 substrate, but part of R-warfarin metabolized by CYP2C19.
- CYP2C9 PMs may potentially be at risk for high exposure if also CYP2C19 PMs or inhibited via CYP2C19

Clinical relevance

Proguanil/ Chlorproguanil

- ~50% metabolized via CYP2C19 (cycloguanil/ chlorcycloguanil formation; active). 2-fold difference in exposure between EMs and PMs
- Gene dose effect in pharmacokinetics [Coller et al 1997, Gross et al 1997]
- But, CYP2C19 status did not correlate with number of malaria breakthrough episodes in Tanzanian patients (s.s. effect/ parent drug may have an effect) [Skjelbo et al 1996]

Clinical relevance



Andersson et al 1990

Clinical relevance

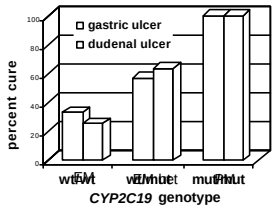
Diazepam

- Wide therapeutic window
- ~50% metabolized via CYP2C19 (demethylation) – only 2-fold difference in exposure between EMs and PMs
- No inhibition of diazepam metabolism in PMs
- Diazepam metabolism less inhibited by omeprazole in Chinese (21%) than in Caucasians (38%) [Caraco et al 1995]
- Extent of decreased diazepam clearance with CYP2C19 inhibition correlates with baseline diazepam clearance in EMs

Clinical relevance

Omeprazole

- Small published studies suggest a gene-dose effect



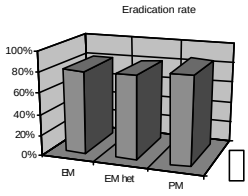
n = 28, 25, 9; 20 mg

Furuta et al 1998

Clinical relevance

Omeprazole

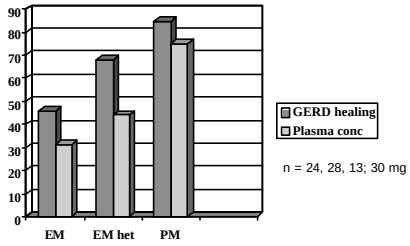
- AZ data set showed no significant gene-dose effect



n = 67, 119, 39; 40 mg

Clinical relevance

Lansoprazole



n = 24, 28, 13; 30 mg

Furuta et al 2002

12th International Symposium on Microsomes and Drug Oxidations, 1998
"Assessment of 2C19 activity" - Summary

	Safe	Easy	Discrimi-nating
Mehenytoin	No	Acc	Yes/No
Proguanil	Yes?	Yes	Yes/No
Diazepam	No	Yes	Yes/No
Omeprazole	Yes	Yes	Yes/No
Lansoprazole	Yes	Yes	Yes/No
Omeprazole-enantiomer	Yes	No	Yes/No?
Genotyping	Yes	Acc	Yes?/No?

12th International Symposium on Microsomes and Drug Oxidations, 1998
"Assessment of 2C19 activity" - Conclusions

- Several possible candidates
- Classical mephenytoin test - acceptable, but limitations
- Genotyping - uncertain
- **Omeprazole**, probe of choice - easily and widely used

Conclusions; 2004

- CYP2C19 – very well characterized enzyme (~10 defective alleles)
- Reliable *in vitro/ in vivo* correlations
- Reliable genotype/ phenotype correlations, except overlap between EM het and EM homo
- Bridging between ethnic groups appropriate
- Genotyping should include minimum *2 &*3, but preferably also *4 -*6 (Caucasians)
- Sometimes clinically relevant consequences (e.g., decrease the dose of TCAs and some other drugs in PMs to decrease adverse effects, but increase dose of PPIs in EM homo to increase efficacy, especially in the more severe patients)